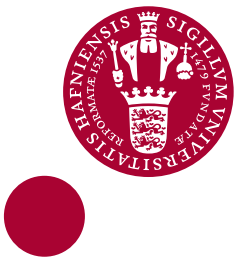

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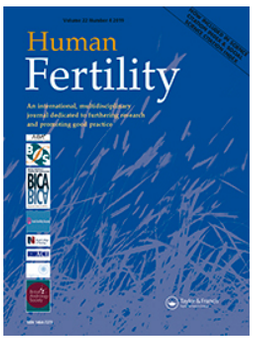

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ORIGINAL ARTICLE

Psychiatric disorders in women and men up to five years after undergoing assisted reproductive technology treatment – a prospective cohort study

Helena Volgsten[a], Lone Schmidt[b], Agneta Skoog Svanberg[a], Lisa Ekselius[c] and Inger Sundström Poromaa[a]

[a]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; [b]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [c]Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden

ABSTRACT

This is a prospective cohort study with the objective to describe psychiatric disorders, such as any mood and anxiety disorders, in both women and men five years after assisted reproductive technology (ART). The Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), was used as the diagnostic tool to evaluate psychiatric disorders. Logistic regression analysis was used to calculate odds ratios (ORs) and confidence interval (CI) for factors associated with psychiatric disorders at the follow-up. Overall, 278 (63.3%) women and 183 (41.7%) men filled in and returned the questionnaire. Approximately 11.5% of women and 5.5% of men fulfilled the criteria for any psychiatric diagnosis. Of these, any mood disorder was present in 9.4% of women and 4.4% of men. The major risk factor for mood or anxiety disorders at follow-up was mood or anxiety disorders at the time of the index ART. Mood disorders were not more common in women who remained childless after ART. In conclusion, these findings indicate that psychiatric disorders at five years follow-up after ART are less common than at the baseline assessment in conjunction with the ART.

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Assisted reproductive technology; cohort study; depression; follow-up; infertility; psychiatric disorders

Introduction

Undergoing medically assisted reproduction (MAR) treatment is a psychological burden for the infertile couples. Previous studies of self-reported depressive symptoms suggest that these symptoms are common and that infertile women suffer from more depressive symptoms than their male partners (Chiaffarino et al., 2011; Peterson, Sejbaek, Pirritano, & Schmidt, 2014). Furthermore, six months and one year later, symptoms of depression are more common in women after unsuccessful treatment (Lund, Sejbaek, Christensen, & Schmidt, 2009; Verhaak, Smeenk, van Minnen, Kremer, & Kraaimaat, 2005). Screening for depressive and anxiety symptoms is important, as women and men with high levels of depressive symptoms may need referral to specialized psychosocial care (Gameiro et al., 2015).

However, in order to establish which patients suffer from clinically relevant mood or anxiety disorders (i.e. those in need of cognitive behavioural therapy and antidepressant treatment) structured psychiatric interviews are needed. Studies assessing mood disorders in both women and men undergoing assisted reproductive technology (ART) treatment by the use of structured clinical interviews are scarce. A prospective study, with the baseline assessment prior to treatment, suggested a high prevalence of depressive disorders in both women and men during ART (Holley et al., 2015). These results are in accordance with our previous study (Volgsten, Skoog Svanberg, Ekselius, Lundkvist, & Sundström Poromaa, 2008), indicating that the prevalence of mood disorders is higher in women and men undergoing ART treatment, than in the general population (Kessler et al., 1994; Kringlen, Torgersen, & Cramer, 2001).

Longitudinal prospective follow-up studies describing symptoms of depression and/or anxiety in women after ART, and in relation to treatment outcome, are few and the results are inconsistent. A follow-up study three to five years after the last ART treatment found that levels of depression and anxiety symptoms in women were lower than during treatment and had returned to baseline levels in women who remained childless (Verhaak, Smeenk, Nahuis, Kremer, & Braat, 2007). Another study indicated more depressive symptoms in women 4–5.5 years after unsuccessful treatment than in women with successful treatment

CONTACT Helena Volgsten helena.volgsten@kbh.uu.se Department of Women's and Children's Health, Uppsala University, 751 85 Uppsala, Sweden

outcomes (Johansson et al., 2009). However, a follow-up after up to nine years after treatment failure showed no more depressive symptoms than compared to the normative sample (Bryson, Sykes, & Traub, 2000).

Again, less is known about psychiatric disorders, such as mood and anxiety disorders. A register-based study from Denmark suggested that women who remained childless were at increased risk of psychiatric disorders compared to women who conceived (Baldur-Felskov et al., 2013). The risk of hospitalization for psychiatric disorders was higher in women after unsuccessful treatment than in women with successful outcome after MAR in other register-based studies (Klemetti, Raitanen, Sihvo, Saarni, & Koponen, 2010; Yli-Kuha et al., 2010). Notably, in the population-based study by Klemetti et al. (2010) no increased risk of psychiatric disorders was found in the male partners. However, register-based studies are only able to capture the patients who have actually sought medical care for their depressive episode or anxiety disorder.

As many individuals with clinically relevant depression remain undiagnosed, prospective studies describing psychiatric disorders in both women and men after ART treatment in clinical settings are needed. Given this lack of information, this prospective cohort study was undertaken to investigate psychiatric morbidity in both women and men up to five years after undergoing ART treatment. We hypothesized that prevalence rates of mood and anxiety disorders would decrease five years after ART, but that women still would be more afflicted than men. A secondary aim was to describe risk factors for mood and anxiety disorders five years after ART, with the hypothesis that previous psychiatric morbidity, and childlessness would increase the risk for mood and anxiety disorders at the follow-up.

Materials and methods

Study population and setting

In our previous prospective study (Volgsten et al., 2008), undertaken between 2005 and 2007, all female and male partners in consecutive couples undergoing ART treatment at the Centre of Reproduction, Uppsala University Hospital, Sweden, were invited to participate. The Centre of Reproduction is public, and infertile couples were offered three subsidized ART treatments at the time of the study. Overall, 862 (79.0%) participants were included in the baseline study and the response rates were 439 (80.5%) women and 423 (77.6%) men. Between 4.5 and 5 years later the same couples were sent follow-up questionnaires by mail to the female home address ($n = 439$). All participants had previously consented to be contacted for this follow-up study. Socio-demographic data were collected by asking the participants to fill in a separate questionnaire. A question about previous history of depression was added to the follow-up questionnaire. Furthermore, a question about sick-leave of at least two weeks due to psychological consequences of the childlessness or fertility treatment was supplemented (Schmidt, 2006). The outcome of treatment after ART was collected from the medical records of all women who did or did not participate in the follow-up study by the first author (HV).

Psychiatric assessment

Diagnoses of psychiatric disorders were assessed by use of the Primary Care Evaluation of Mental Disorders (PRIME-MD) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Fourth Edition. The PRIME-MD system, which is fully described elsewhere (Spitzer et al., 1994), consists of two components: a one-page patient questionnaire and a 12-page clinician evaluation guide, which is a structured interview guide to be used when evaluating the responses on the questionnaire. Only those modules that are indicated by the participant on the questionnaire, containing 24 questions, are administered. The PRIME-MD system evaluates the presence of 20 possible psychiatric disorders, of which this follow-up study focused on the following diagnoses: major depressive disorder, dysthymia, partial remission of major depressive disorder, generalized anxiety disorder and panic disorder. Minor depressive disorder and anxiety not otherwise specified (NOS) are considered 'subthreshold' diagnoses and have fewer symptoms than required for a specific DSM-IV diagnosis but was included in the study as they are also associated with considerable disability.

Study design

This prospective cohort study was conducted with individual questionnaires for women and men sent to the female home address. Women and men were asked for consent to participate in the study and to complete and return the PRIME-MD questionnaire by mail in an individual prepaid envelope. Two reminders were sent within about three weeks. Along with the questionnaire, women and men were asked to provide name, date of birth, individual cell phone number, and a signed informed consent allowing for an interview

by phone. Participants were considered to be screen-positive if a response to any key question indicated a psychiatric disorder. Screen-negative were those whose responses on the questionnaire did not include items suggesting these symptoms. To confirm a diagnosis, an interview by phone using a computerized version of the clinician evaluation guide was conducted with screen-positive women and men. As all participants provided their individual mobile phone numbers, female and male partners were interviewed separately, on different occasions. The interview was conducted within 21 days after screening. All participants with confirmed diagnosis were offered referral to psychiatric specialist. In case of a diagnosis, the participant was asked about previous history of depression and current antidepressant therapy or psychotherapy, such as counsellor or psychologist. The interviews by phone were performed by the first author (HV), who had both clinical and research experience from previous study (Volgsten et al., 2008). The study was approved by the Institutional Review Board (IRB) of Uppsala University, Sweden (Dnr 2005:029).

Statistical analyses

Continuous variables were compared by the use of independent *t*-tests and presented as mean ± SD. Frequencies were compared between groups using the chi square test. Data were compared between women and men with psychiatric disorders and women and men with no disorder; the latter group consisted of screen-negative and screen-positive women and men in whom no psychiatric diagnosis was established during the telephone interview. Data were also compared between women and men with psychiatric disorders in the previous baseline study (Volgsten et al., 2008) and women and men with psychiatric disorders in the follow-up. Furthermore, data between women participating and not participating in the present follow-up study were compared. All statistical analyses were performed using SPSS 22.0. A *p*-value less than 0.05 was considered significant. Multivariable logistic regression analysis was used to calculate adjusted odds ratios (ORs) and 95% confidence interval (CI) for factors associated with psychiatric disorders at the follow-up. The evaluated factors were age and BMI (for women) at follow-up, psychiatric disorders at baseline assessment, same-partner relationship, and whether the participants were living with or without children at follow-up.

Results

Study population

A total of 439 couples ($n = 878$) were eligible for the follow-up study. Of these, 461 (52.5%) subjects agreed to participate and filled out the PRIME-MD questionnaire and consented to an interview. Overall, the response rates were 278 (63.3%) women and 183 (41.7%) men. Among the 183 men who participated, 181 were living with a female partner who also consented to participation. Among participants who filled out the questionnaire, 115 (41.4%) women and 41 (22.4%) men were screen-positive for psychiatric disorders and consented to the follow-up psychiatric interview. Of these, 26 women and six men were screen-positive but could not be reached within the stipulated 21-day period.

At follow-up, most women (92.8%) and men (98.9%) were living with the same partner as they did when included in the baseline study and 78.0% of women stated they had ended ART. Furthermore, the majority of women and men declared they were living with children (91.7% and 93.4%, respectively) (Table 1). Among women living with children, 80.9% had a live birth; the majority following ART (71.6%) and 28.0% after spontaneous pregnancy, or both. Furthermore, 24 (8.6%) women and five men (2.7%) were living with children from the partners' previous relationship, and 19 (6.8%) women and 13 (7.1%) men had adopted a child. Almost one of five (19.1%) women had no live birth at follow-up (Volgsten & Schmidt, 2017). Of those declining to participate in this follow-up study, 51 (31.6%) women and 31 (12.1%) men had a psychiatric disorder at baseline ($p < 0.05$). No difference in live birth rate after ART treatment was noted between women who did or did not participate in the follow-up study (data not shown).

Table 1. Sociodemographic and medical characteristics of the study population.

	Women ($n = 278$)	Men ($n = 183$)
Age, years (mean ± SD)	38.3 ± 3.9	39.7 ± 4.7
Body Mass Index, kg/m^2	24.9 ± 4.5	–
Employment status		
Employed	217 (78%)	170 (92.9%)
Student	15 (5.4%)	1 (0.5%)
Parental leave	28 (10.1%)	4 (2.2%)
Unemployed	9 (3.3%)	3 (1.6%)
Sick-leave	7 (2.5%)	5 (2.7%)
Living with same partner	258 (92.8%)	181 (98.9%)
Living with children	255 (91.7%)	171 (93.4%)
ART		
Terminated treatment	217 (78%)	150 (82.4%)
Not decided whether to continue treatment	42 (15.1%)	19 (7.1%)
Want or plan to continue treatment	19 (6.8%)	13 (10.4%)
Sick-leave during ART	40 (14.4%)	3 (1.6%)
Counsellor/psychologist at follow-up	18 (6.5%)	6 (3.3%)

Mood and anxiety disorders at follow-up

Rates of any mood and/or anxiety disorders detected by the structured psychiatric interview at the follow-up are summarized in Table 2. Of the 278 women in the study sample, 32 (11.5%) women had a psychiatric diagnosis, whereas the corresponding figure for the 183 men was 10 (5.5%). The difference between women and men was significant ($p < 0.05$).

At follow-up, 40 (14.3%) women and three (1.6%) men declared they had been on sick-leave due to psychological consequences of the fertility treatment or childlessness. Similarly, at follow-up, 18 (6.5%) women and six (3.3%) men stated that they were in contact with counsellor/psychologist.

Risk factors for mood and anxiety disorders at the follow-up

Among the women and men who participated in the follow-up, a total of 76 women (27.3%) and 11 men (6.0%) had any psychiatric disorder at the baseline assessment ($p < 0.05$). Of participants with any psychiatric diagnosis at follow-up, every second woman (50.0%), had a diagnosis five years earlier ($p < 0.003$) and almost one in three men (30.0%) ($p < 0.02$) (Table 3). Following adjustment for age, BMI, same-partner relationship, and whether or not participants were living with a child at follow-up, psychiatric morbidity at the baseline assessment was the primary predictor of mental health at the follow-up in women (adjusted OR 3.02, 95% CI 1.41–6.44) and men (adjusted OR 9.20, 95% CI 1.83–46.09), respectively. Whether the participants were living with children or not, had no influence in these analyses.

Table 2. Prevalence of psychiatric disorders detected by PRIME-MD at five-year follow-up.

	Women ($n = 278$)	Men ($n = 183$)
Any psychiatric diagnosis at baseline	76 (27.3%)	11 (6.0%)
Any psychiatric diagnosis at follow-up[a]	32 (11.5%)	10 (5.5%)
Any depressive disorder at follow-up	26 (9.4%)	8 (4.4%)
Major depressive disorder	16 (5.7%)	6 (3.3%)
Dysthymia	2 (0.7%)	4 (2.2%)
Partial remission of major depressive disorder	5 (1.8%)	1 (0.5%)
Minor depressive disorder	11 (4%)	2 (1.1%)
Any anxiety disorder at follow-up	15 (5.4%)	5 (2.7%)
Anxiety NOS[b]	8 (2.9%)	1 (0.5%)
Generalized anxiety disorder	5 (1.8%)	3 (1.6%)
Panic disorder	3 (1.1%)	3 (1.6%)

[a]Study participants can have one or more psychiatric diagnoses within any mood and/or any anxiety disorders.
[b]NOS: not otherwise specified.

Discussion

This is to our knowledge the first prospective cohort study to describe the prevalence of psychiatric disorders in both women and men up to five years after ART treatment. Approximately 11.5% of the women and 5.5% of the men in the present study fulfilled criteria of any full or subthreshold psychiatric disorder at the time of the follow-up. These findings indicate that psychiatric disorders five years after ART are less common than at the index ART treatment, and not more common than in the general population (Kessler et al., 1994; Kringlen et al., 2001), but women are still more affected than men. The low prevalence of psychiatric disorders is in accordance with previous long-term studies, demonstrating lower burden of depressive symptoms at follow-up in comparison with the initial ART treatment (Verhaak et al., 2007; Stewart et al., 2015). Moreover, few participants reported contact with psychologist/psychiatrist, in contrast to other follow-up studies (Johansson et al., 2009).

The major risk factor for mood or anxiety disorders at the follow-up was mood or anxiety disorders at the time of the index ART. In contrast to our hypothesis, we found that mood disorders were not more common in women who remained childless after ART treatment. It should be noted that one of the study objectives was to compare the mental health status between couples who were living with children and those who remained childless. Surprisingly though, the majority of our participants were still living with the same partner at the follow-up, and more than ninety percent were living with children. Thus, whilst previous studies have emphasized that women who remain

Table 3. Any psychiatric diagnosis among women and men in logistic regression.

	Women ($n = 278$)				Men ($n = 183$)			
	Psychiatric diagnosis				Psychiatric diagnosis			
	Yes = 32	No = 246	Adjusted odds ratio (OR)	95.0% confidence interval	Yes = 10	No = 173	Adjusted odds ratio (OR)	95.0% confidence interval
Previous psychiatric diagnosis[a]								
Yes	16 (50.0)	58 (23.6)	3.64*	1.63–8.10	3 (30.0)	8 (4.6)	4.69*	0.79–27.83
No	16 (50.0)	188 (76.4)	–	–	7 (70.0)	165 (95.4)	–	–

*$p < 0.05$.
[a]Missing items = 2.

childless after ART report more depressive symptoms, especially if they have a sustained child-wish (Gameiro et al., 2014; Gameiro et al., 2016; Vikstrom, Josefsson, Bladh, & Sydsjö, 2015), our study was clearly not powered to elucidate this question, given the few men and women who remained childless five years after the ART. However, our findings are not due to attrition as no difference in live birth rate after ART was found between women who did or did not participate in this five-year follow-up.

The major strength of the present study was the longitudinal prospective design in a clinical setting and the inclusion of both women and men. Another strength was the use of a structured psychiatric interview. Data based merely on self-report questionnaires are affected by positive selection bias (Pinborg, Hougaard, Nyboe Andersen, Molbo, & Schmidt, 2009) and are not indicative of a psychiatric diagnosis (Holley et al., 2015). However, some limitations need to be mentioned. First, this follow-up conducted up to five years after ART treatment had a high drop-out rate among men, especially among those who had psychiatric disorders at baseline and therefore these results must be interpreted with caution. Furthermore, there was no access to information of the mental health status in women and men who declined participation and information whether they were living with or without children. However, while a limitation was the high drop-out rate among men, other drop-out analyses, such as live birth rate after ART suggested no differences between participating and non-participating couples.

In conclusion, these findings indicate that psychiatric disorders up to five years after ART are less common than at baseline inclusion. Most participants were living with the same partner and the majority had found ways to overcome childlessness. While the index ART treatment was a psychological burden for couples, psychiatric morbidity was less common at the five-year follow-up.

Disclosure statement

No potential conflict of interest was reported by the authors.

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